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Seladelpar (MBX-8025), a selective PPAR-δ agonist, in patients with primary biliary cholangitis with an inadequate response to ursodeoxycholic acid: a double-blind, randomised, placebo-controlled, phase 2, proof-of-concept study

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Summary

Background Many patients with primary biliary cholangitis have an inadequate response to first-line therapy with ursodeoxycholic acid. Seladelpar is a potent, selective agonist for the peroxisome proliferator-activated receptor-delta (PPAR-δ), which is implicated in bile acid homoeostasis. This first-in-class study evaluated the anti-cholestatic effects and safety of seladelpar in patients with an inadequate response to ursodeoxycholic acid.

Methods The study was a 12-week, double-blind, placebo-controlled, phase 2 trial of patients with alkaline phosphatase of at least 1·67 times the upper limit of normal (ULN) despite treatment with ursodeoxycholic acid. Patients, recruited at 29 sites in North America and Europe, were randomly assigned to placebo, seladelpar 50 mg/day, or seladelpar 200 mg/day while ursodeoxycholic acid was continued. Randomisation was done centrally (1:1:1) by a computerised system using an interactive voice–web response system with a block size of three. Randomisation was stratified by region (North America and Europe). The primary outcome was the percentage change from baseline in alkaline phosphatase over 12 weeks, analysed in the modified intention-to-treat (ITT) population (any randomised patient who received at least one dose of medication and had at least one post-baseline alkaline phosphatase evaluation). This study is registered with ClinicalTrials.gov (NCT02609048) and the EU Clinical Trials Registry (EudraCT2015-002698-39).

Findings Between Nov 4, 2015, and May 26, 2016, 70 patients were screened at 30 sites in North America and Europe. During recruitment, three patients treated with seladelpar developed fully reversible, asymptomatic grade 3 alanine aminotransferase increases (one on 50 mg, two on 200 mg), ranging from just over five to 20 times the ULN; as a result, the study was terminated after 41 patients were randomly assigned. The modified ITT population consisted of 12 patients in the placebo group, 13 in the seladelpar 50 mg group, and 10 in the seladelpar 200 mg group. Mean changes from baseline in alkaline phosphatase were –2% (SD 16) in the placebo group, –53% (14) in the seladelpar 50 mg group, and –63% (8) in the seladelpar 200 mg group. Changes in both seladelpar groups versus placebo were significant (p<0·0001 for both groups *vs* placebo), with no significant difference between the two seladelpar groups (p=0·1729). All five patients who received seladelpar for 12 weeks had normal alkaline phosphatase values at the end of treatment, based on a central laboratory ULN for alkaline phosphatase of 116 U/L. The most frequently reported adverse events were pruritus (16%; one patient on placebo, four on seladelpar 50 mg, and one on seladelpar 200 mg), nausea (13%; one patient on placebo, three on seladelpar 50 mg, and one on seladelpar 200 mg), diarrhoea (10%; two patients on placebo, one on seladelpar 50 mg, and one on seladelpar 200 mg), dyspepsia (8%; two patients on seladelpar 50 mg and one on seladelpar 200 mg), muscle spasms (8%; three patients on seladelpar 200 mg), myalgia (8%; one patient on placebo and two on seladelpar 200 mg), and dizziness (8%; one patient on placebo and two on seladelpar 50 mg).

Interpretation Seladelpar normalised alkaline phosphatase levels in patients who completed 12 weeks of treatment. However, treatment was associated with grade 3 increases in aminotransferases and the study was stopped early. The effects of seladelpar should be explored at lower doses.

Funding CymaBay Therapeutics.

Introduction

Primary biliary cholangitis, formerly known as primary biliary cirrhosis, is a chronic, progressive, cholestatic liver disease.[1] The liver shows a lymphocytic infiltration with progressive damage to lobular bile ducts, which leads to impaired bile flow. Although the condition is presumed to have an autoimmune aetiology, chronic cholestasis drives the pathophysiological process, and can lead to cirrhosis.

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Research in context

Evidence before this study

Primary biliary cholangitis is a progressive cholangitic liver disease which, if untreated, progresses to cirrhosis and death or liver transplantation. We searched PubMed with no language limitations using the terms "primary biliary cirrhosis", "primary biliary cholangitis", "liver cirrhosis, biliary", "trial", "drug", and "therapy". We also searched the ClinicalTrials.gov database for clinical trials in primary biliary cirrhosis or primary biliary cholangitis. Both searches were censored on April 20, 2017. In primary biliary cholangitis, the standard of care for over 20 years has been the hydrophilic bile acid ursodeoxycholic acid. The response to ursodeoxycholic acid is variable, with a substantial proportion of patients (up to 40%) having an inadequate response in terms of liver biochemistry improvement and reduced survival. Non-response to ursodeoxycholic acid is more frequent in younger patients, increasing the level of unmet need in primary biliary cholangitis. Appreciation of the need for better therapy in patients with high-risk primary biliary cholangitis led to the development of the second-line therapy, obeticholic acid, which was approved for use in both the USA and Europe in 2016 in patients showing an inadequate response to ursodeoxycholic acid. Obeticholic acid (a synthetic bile acid) acts via agonism of the farnesoid X receptor, which regulates bile acid homoeostasis. However, obeticholic acid has two important limitations as second-line therapy. The first is that it is itself incompletely effective, with 50% of high-risk patients treated with it showing inadequate response in a phase 3 trial. The second is that it can cause worsening of pruritus (a key symptom of primary biliary cholangitis) and induce pruritus in previously symptom-free patients. Given the association between disease (and thus the need for obeticholic acid) and pruritus, this represents an important potential limitation in its use. With these limitations, the search for additional and alternative second-line therapies is ongoing.

Added value of this study

This study is a first-in-class, randomised, placebo-controlled trial of a PPAR-δ agonist in primary biliary cholangitis. The mode of action of the drug on bile acid synthesis and inflammation, and its non-bile-acid-based structure make it an intuitive agent to explore as second-line therapy in primary biliary cholangitis. The trial had two important positive findings and one caution. The positive finding, albeit based on a limited number of patients, is a normalisation of liver biochemistry in patients reaching 12 weeks of therapy. Improvement was also seen in other cholestatic markers suggesting a true anti-cholestatic effect and the mechanism of action appeared to be through reduced bile acid synthesis as predicted. The second positive finding was that there was no evidence of pruritus as a side-effect. However, a note of caution should be made since three patients showed rapidly reversible alanine aminotransferase (ALT) elevations.

Implications of all the available evidence

Seladelpar has the potential to be an improved second-line therapy in high-risk primary biliary cholangitis. A study at lower doses is underway to identify effective doses that do not cause ALT elevation (NCT029556020 and EudraCT 2016-002996-91). If the risk of ALT elevation can be eliminated while retaining efficacy, the drug offers the potential for routine liver biochemistry normalisation in high-risk patients with primary biliary cholangitis.

Primary biliary cholangitis occurs predominantly in women and is often first suspected by persistent elevations of serum alkaline phosphatase on routine blood tests. Patients progress at varying rates, although a diagnosis at a younger age appears to negatively affect prognosis.[2] Inadequate medical treatment puts patients at risk of liver death and the need for liver transplantation. Two drugs, ursodeoxycholic acid and obeticholic acid, have been approved to medically treat primary biliary cholangitis.[3,4]

Ursodeoxycholic acid, a non-cytotoxic bile acid, has been the mainstay of therapy for more than 20 years.[1,5] However, up to 40% of patients have persistent elevation of alkaline phosphatase or bilirubin or both despite treatment with ursodeoxycholic acid and are considered inadequate responders.[6] These patients have a worse hepatic transplant-free survival rate compared with ursodeoxycholic acid responders.[7,8] Consequently, alkaline phosphatase, when combined with total bilirubin, are now considered surrogate markers of primary biliary cholangitis severity that predict the progression of the disease.[9]

Obeticholic acid, a synthetic analogue of chenodeoxycholic acid, was recently conditionally approved based on its ability to decrease alkaline phosphatase concentrations when used as an add-on therapy in patients with primary biliary cholangitis who are inadequate responders to ursodeoxycholic acid. It is also approved for patients who cannot tolerate ursodeoxycholic acid (around 5% of patients). By contrast with ursodeoxycholic acid, obeticholic acid activates the farnesoid X receptor[10] and exerts its effects through a distinct mechanism of action. However, about 50% of patients with primary biliary cholangitis still lack an adequate response to a combination of ursodeoxycholic acid and obeticholic acid.[4] Also, obeticholic acid has been associated with inducing or worsening pruritus, a characteristic symptom of primary biliary cholangitis, which can require treatment interruption.[4] Accordingly, there is still a substantial medical need to develop new therapies for primary biliary cholangitis.[11]

Peroxisome proliferator-activated receptors (PPARs) are nuclear receptors that direct the transcription of genes involved in bile acids or sterols, lipids, and glucose metabolism, as well as inflammation.[12–14] Three PPAR subtypes—α, γ, and δ—are known,[13] each of which have

their own distinct but overlapping cellular expression, target genes, pathway regulation, and biological functions. Fenofibrate, a PPAR-α agonist,[15] and bezafibrate, a pan-PPAR agonist,[16] have shown promising activity in decreasing markers of cholestasis in patients with primary biliary cholangitis, although there are concerns about potential toxic effects. Their primary effects result from decreasing hepatocellular bile acid concentrations by regulation of genes responsible for bile acid synthesis and transport.[17,18] Seladelpar (MBX-8025) is an oral, once-daily, potent, and selective PPAR-δ agonist.[12] Like PPAR-α, PPAR-δ is also expressed in hepatocytes,[19] where it controls genes involved in bile acid homoeostasis. Seladelpar downregulates the expression of *cyp7a1* which encodes cholesterol 7α-hydroxylase (appendix p 10), the enzyme that hydroxylates cholesterol in the first step in the synthesis of bile acids. Unlike PPAR-α, for which liver expression is mainly restricted to hepatocytes,[20] PPAR-δ is also expressed in cholangiocytes,[21] Kupffer cells, and hepatic stellate cells,[19] and its activation in these cells has implications for modifying progression of primary biliary cholangitis. Cholangiocytes use PPAR-δ[21] to regulate transporters involved in the absorption and secretion of bile components. Seladelpar regulates the cholesterol transporter ABCG5/ABCG8 in mouse liver (appendix p 11) and another PPAR-δ agonist was shown to increase bile flow three-fold in mice.[22] Activation of PPAR-δ also results in anti-inflammatory effects in macrophages,[23] including Kupffer cells.[24] Seladelpar, in a mouse model, reduces markers of liver inflammation, including reductions in macrophage numbers, reductions in fibrosis, and reduction of other markers of stellate cell activity.[25] Thus, the rationale for assessing PPAR-δ as a target for cholestatic diseases includes the impact on bile acid retention, cholangiocyte function, and anti-inflammatory and anti-fibrotic effects on Kupffer and stellate cells.

Although primary biliary cholangitis is an autoimmune disease, the ensuing cycle of biliary epithelial injury, cholestasis, and fibrosis is thought to be substantially more important as a determinant of outcome for patients, with multiple strands of evidence supporting the importance of biliary epithelial responses to injury in driving the clinical course. The effects on cholestasis, inflammation, and fibrosis resulting from PPAR-δ agonism are therefore predicted to affect disease progression. In healthy volunteers, seladelpar decreased the intestinal absorption of cholesterol, decreased the synthesis of cholesterol, and modulated bile acid synthesis.[26] In patients with mixed dyslipidaemia[12] or homozygous familial hypercholesterolaemia,[27] seladelpar reduced low-density lipoprotein cholesterol (LDL-C) and also induced sustained decreases in biochemical markers of cholestasis, such as alkaline phosphatase, γ-glutamyl transpeptidase (GGT), and total bilirubin.[27] Seladelpar treatment also decreased biochemical markers of inflammation,[12] an activity that could be of benefit to treat autoimmune diseases such as primary biliary cholangitis. So far, about 140 patients have received seladelpar at doses ranging from 50 mg/day to 200 mg/day for up to 12 weeks.[12,26,27] Seladelpar appeared safe and well tolerated with no specific adverse reaction definitively associated with the drug.[12,26,27] Seladelpar was not associated with drug-induced pruritus.[12,26,27]

The aim of the present study was to explore the efficacy and safety of seladelpar in patients with primary biliary cholangitis who are inadequate responders to ursodeoxycholic acid treatment.

Methods

Study design and participants

See Online for appendix

This study was an international, multicentre, double-blind, randomised, placebo-controlled, parallel, dose-ranging trial of 18 weeks' duration. All patients were to continue their ursodeoxycholic acid treatment at the same dose during the study. After signing informed consent, patients underwent a 4-week screening period to confirm eligibility.

The study enrolled patients aged 18–75 years with a diagnosis of primary biliary cholangitis at 29 centres in North America and Europe. The diagnosis required the presence of at least two of the following criteria: a history of alkaline phosphatase above the upper limit of normal (ULN) for at least 6 months, a positive autoantibody test (anti-mitochondrial antibody >1:40 on immunofluorescence or M2 positivity by enzyme-linked immunosorbent assay or positive anti-nuclear antibodies specific to primary biliary cholangitis), and a documented liver biopsy consistent with primary biliary cholangitis. Patients were required to be on a stable and recommended dose of ursodeoxycholic acid for the past 12 months and to have an alkaline phosphatase of at least 1·67 times the ULN.

Patients were excluded if they had any other liver conditions, or any medical condition that would preclude full participation, confound the results, or compromise their safety. Other exclusions were alanine aminotransferase (ALT) or aspartate aminotransferase (AST) concentrations more than three times the ULN, total bilirubin more than two times the ULN, and creatine kinase or serum creatinine above the ULN. The use of colchicine, methotrexate, azathioprine, or systemic steroids within 2 months before screening was not permitted. Patients taking fibrates or simvastatin were also excluded, as well as any patients on experimental primary biliary cholangitis treatment, including obeticholic acid. For patients of reproductive age, appropriate methods of contraception were to be used.

The study was approved by the relevant health authorities of the participating countries (Canada, Germany, Poland, the UK, and the USA) and independent ethics committees. The study was monitored by an independent data and safety monitoring board. [A: additional?] All patients provided written informed consent to participate. The study was done in accordance

with the principles of The Declaration of Helsinki and Good Clinical Practice Guidelines.

Randomisation and masking

Eligible patients were randomly assigned (1:1:1) after the 4-week screening period to placebo, seladelpar 50 mg, or seladelpar 200 mg orally once daily using a centralised online response system (interactive web response system) and entered the double-blind 12-week treatment period. The randomisation was stratified by region (North America and Europe) and used a block size of three. A third-party vendor (Perceptive Informatics, Waltham, MA, USA) was responsible for generating the randomisation scheme and managing randomisation activities. Each patient was assigned a unique study identification number by the interactive web response system, and this triggered masked, patient-specific, on-demand shipment of the study drug. To maintain masking, all study medication capsules were identical in appearance. Patients, investigators, clinical trial site staff, and sponsor staff directly involved with the study were masked to treatment assignment throughout the study. Masking of medication was completed by the masking of alkaline phosphatase values. GGT, ALT, and AST values, which were necessary for safety monitoring, were not masked.

Procedures

During treatment, site visits occurred at weeks 2, 4, 8, and 12, and telephone contact was made at weeks 6 and 10. A follow-up assessment took place 2 weeks after the end of treatment.

Participants with creatine kinase of more than five times the ULN and musculoskeletal symptoms were discontinued from the study drug and withdrawn from the study; those with creatine kinase of more than five times the ULN without musculoskeletal symptoms were to be retested within 48 h, and if creatine kinase was still above the ULN, patients were to discontinue study drug and were withdrawn from the study. Patients were also to discontinue the study drug in the event of hepatic decompensation. For individuals with creatine kinase above 2·5 times but less than five times the ULN with musculoskeletal symptoms, the study drug was to be interrupted until resolution, at which point the drug could be resumed at a lower dose. Patients with creatine kinase above 2·5 times but less than five times the ULN without musculoskeletal symptoms were to be retested within 72 h, and if still raised, the study drug was to be continued at a lower dose.

Safety was assessed throughout the study by physical examination, ECG, the monitoring of adverse events and treatment-emergent adverse events, the recording of concomitant medications, and laboratory assessments. The severity of adverse events and laboratory abnormalities were graded as per the Common Terminology Criteria for Adverse Events (version 4.03). The data and safety monitoring board periodically reviewed safety data [A: edi...?]. A central laboratory did haematological and biochemical determinations (Medpace Reference Laboratories; Cincinnati, OH, USA, and Leuven, Belgium). Seladelpar and its metabolites were analysed by MicroConstants (San Diego, CA, USA).

Outcomes

The primary efficacy assessment was change from baseline in alkaline phosphatase concentrations over 12 weeks. Secondary assessments were tolerability and safety and additional efficacy parameters. Secondary efficacy assessments included a composite of an alkaline phosphatase value less than 1·67 times the ULN with normal total bilirubin and a decrease of at least 15% from baseline; an evaluation of published primary biliary cholangitis response criteria (Paris I and II, Toronto I and II, and the UK primary biliary cholangitis risk score); AST, ALT, GGT, 5′-nucleotidase, bilirubin (total, conjugated, and unconjugated), bone-specific alkaline phosphatase, triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDL-C), and LDL-C; and pruritus evaluated with a visual analogue score, the 5D-itch questionnaire, and the PBC-40 quality-of-life questionnaire.

Exploratory efficacy measures included serum or plasma concentrations of the following: bile acid precursor 7α-hydroxy-4-cholesten-3-one (C4); high-sensitivity C-reactive protein (hs-CRP); bile acids (ursodeoxycholic acid, cholic acid, chenodeoxycholic acid, deoxycholic acid, and lithocholic acid, their glyco-conjugates and tauro-conjugates); IgM, anti-mitochondrial antibody, and homocysteine; 7α-hydroxy cholesterol; intermediates of cholesterol synthesis (squalene, lanosterol, desmosterol, lathosterol, and 7-dehydrocholesterol); markers of intestinal cholesterol absorption (β-sitosterol, campesterol, and stigmasterol); and cholestanol and coprostanol. In selected centres, shear wave elastography of the liver was done but the results are not reported here. Concentrations of fibroblast-growth factor 19 (FGF-19), an enterokine released after farnesoid X receptor activation, were measured post hoc. Trough plasma concentrations of seladelpar and its metabolites (M1, M2, and M3) were measured at weeks 4 and 12.

Statistical analysis

The safety analysis was done on the safety population, which included any randomised patient who received at least one dose of medication. Efficacy analyses were done on the modified intention-to-treat (mITT) population, which consisted of any randomised patient who received at least one dose of medication and had at least one post-baseline alkaline phosphatase evaluation. It was assumed that the mean percent alkaline phosphatase decrease would not be more than 5% in the placebo group and at least 25% in the seladelpar groups with an SD for the percent change from baseline to end of treatment of 20%. Based on these assumptions, using a two-sided comparison

of means at the alpha 0·05 level of significance with a sample size of 23 patients per group, the study had a 90% power to detect a difference of 20% between the active and placebo groups. To account for up to two patients per group who might be excluded from the mITT population, the planned sample size was 25 patients per group.

Baseline was defined as the mean between screening and baseline (day 1) values for the primary analysis and day 1 as baseline values for other analyses.

Descriptive statistics (ie, means, medians, and measures of dispersion) were to be presented and the last observation carried forward method was used for missing laboratory data. The primary efficacy analysis compared the mean percentage change in alkaline phosphatase concentrations from baseline to end of treatment between the seladelpar 200 mg treatment group and the placebo group. If this analysis was significant, the next comparison was between the seladelpar 50 mg treatment group and the placebo group. For the primary analysis, one-way ANOVA was used. A similar analysis was used for secondary analyses on normally distributed parameters. In the absence of normality, a non-parametric test was used (Wilcoxon). Statistical analyses were done using SAS version 9.4. This study is registered with CinicalTrials.gov (NCT02609048) and the EU Clinical Trials Registry (EudraCT2015-002698-39).

Role of the funding source

CymaBay Therapeutics funded the study and supported the study design, data collection, analysis, and operation of the study. All authors had access to the datasets and statistical analysis plan and had rights to audit data. DJ, PFB, MGS, CLB, and GMH finalised data presentation and had responsibility to submit the manuscript after obtaining agreement from all the authors.

Results

Between Nov 4, 2015, and May 26, 2016, 70 patients were screened. While recruitment was still ongoing, three patients on masked treatment developed grade 3 aminotransferase elevations (ranging from just over five to 20 times the ULN; appendix p 13). All three cases were deemed to be drug related. Consequently, on May 27, 2016, the funder terminated the study and informed study sites, the data and safety monitoring board, and health authorities of its decision. Patients were requested to discontinue their treatment, return to study sites to complete an end-of-treatment visit, and then proceed to a follow-up (off-treatment) end-of-study visit 2 weeks later. As a result, only 41 patients were randomly assigned to a treatment group (figure 1). Two patients did not receive treatment because the study was discontinued after randomisation but before dosing, and one patient developed a variceal bleed after randomisation but before dosing. The remaining 38 patients who received either placebo or seladelpar constituted the safety population. Mean age was 55 years [A: should this be median, as in tabl[illegible] Please add IQR or SD] and most patients were women (table 1). There was an

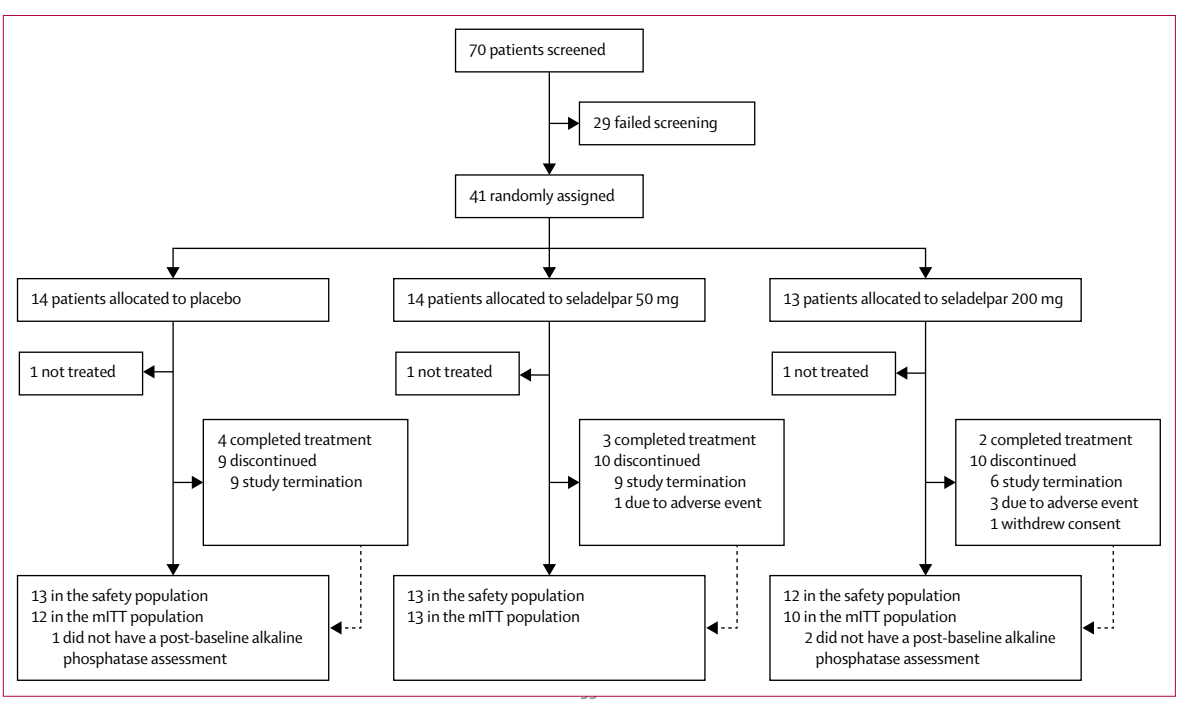

Figure 1: **Trial profile**
mITT=modified intention to treat.

	Placebo group (n=13)	Seladelpar 50 mg group (n=13)	Seladelpar 200 mg group (n=12)
Age (years)	56 (48–61)	55 (49–58)	57 (54–65)
Sex			
Female	12 (92%)	12 (92%)	12 (100%)
Male	1 (8%)	1 (8%)	0
Age at diagnosis (years)	52 (40–55)	49 (41–50)	43 (39–54)
Duration of primary biliary cholangitis (years)	4 (3–11)	7 (3–13)	9 (1–22)
Body-mass index (kg/m²)	28 (6)	24 (5)	27 (4)
Pruritus (visual analogue scale ≥30)	4 (33%)	4 (31%)	5 (50%)
Alkaline phosphatase (U/L)*	233 (73)	312 (95)	248 (89)
Alanine aminotransferase (U/L)	40 (24)	47 (31)	32 (15)
Aspartate aminotransferase (U/L)	36 (12)	37 (18)	32 (11)
γ-glutamyl transferase (U/L)*	183 (123)	220 (152)	104 (41)
Total bilirubin (mg/dL)	0·68 (0·35)	0·73 (0·27)	0·75 (0·38)
Albumin (g/dL)	4·3 (0·4)	4·3 (0·4)	4·1 (0·3)
Platelets (×10³ per μL)	235 (83)	271 (86)	227 (79)
Total ursodeoxycholic acid dose (mg/kg per day)	16 (2)	15 (3)	14 (2)

Data are median (IQR), mean (SD), or n (%). *Data calculated on the efficacy population.

Table 1: **Patient demographics and baseline characteristics**

	Week 0	Week 2	Week 4	Week 8	Week 12
Placebo	0/12	1/12	1/10	1/6	0/4
Seladelpar 50 mg	0/13	2/13	4/8	4/5	3/3
Seladelpar 200 mg	0/10	5/10	5/6	4/4	2/2

*Central laboratory upper limit of normal for alkaline phosphatase is 116 U/L.

Table 2: **Number of patients with normalisation of alkaline phosphatase according to week(s) of treatment***

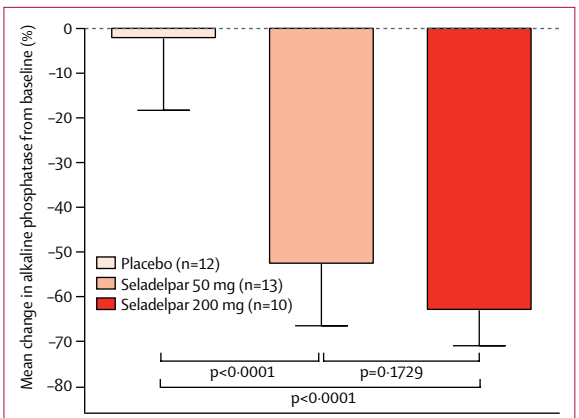

Figure 2: **Mean percentage change in alkaline phosphatase over 12 weeks (last observation carried forward)**
Bars are SD.

imbalance in baseline alkaline phosphatase and GGT concentrations among groups (table 1). Other baseline characteristics were well balanced.

15 patients completed 8 weeks of treatment (six on placebo, five on seladelpar 50 mg, and four on seladelpar 200 mg) and nine patients completed 12 weeks of treatment (four on placebo, three on seladelpar 50 mg, and two on seladelpar 200 mg; table 2).

Alkaline phosphatase changes from baseline over 12 weeks are presented in figure 2. Mean change from baseline in the placebo group was –2% (SD 16). The mean percentage change in alkaline phosphatase in both seladelpar groups was significant compared with placebo, with a decrease from baseline of 53% (SD 14) in the 50 mg group and a decrease from baseline of 63% (8) in the 200 mg group (both p<0·0001 *vs* placebo). There were no clinically relevant or statistically significant differences between the seladelpar groups (p=0·1167). Over 12 weeks, patients on both doses of seladelpar had a rapid decrease in alkaline phosphatase, whereas patients on placebo had stable alkaline phosphatase concentrations (figure 3). Decreases in alkaline phosphatase were recorded after 2 weeks of treatment, the first assessment in the study, with a slower decline up to week 12. All five patients on seladelpar who reached 12 weeks on treatment had normal alkaline phosphatase concentrations by week 12, based on a central laboratory ULN for alkaline phosphatase of 116 U/L (table 2). No patient on placebo had normal alkaline phosphatase levels after 12 weeks. As early as 8 weeks, eight (89%) of nine patients on seladelpar had normal alkaline phosphatase values. For the composite outcome of alkaline phosphatase and total bilirubin, at 12 weeks, all patients on seladelpar and none on placebo were responders (table 2).

Decreases were also noted with seladelpar in the concentrations of other cholestasis-associated enzymes, GGT, and 5′-nucleotidase (appendix p 1). There were no significant differences in the GGT or 5′-nucleotidase changes between the seladelpar groups. The mean percentage changes in total bilirubin, indirect bilirubin, and direct bilirubin are shown in the appendix (p 1). Significant decreases in hs-CRP and in LDL-C were recorded for both seladelpar groups compared with placebo (appendix p 1). The mean percentage changes in HDL-C and triglycerides are also presented in the appendix (p 1).

Over 12 weeks, there were significant decreases in C4, a marker of de-novo bile acid synthesis, in both seladelpar groups (figure 4), with no significant difference between seladelpar groups. The decreases in C4 were accompanied by decreases in 7-α-hydroxy-cholesterol, the precursor of C4 (appendix p 2). The median percentage changes in bile acid concentrations are shown in the appendix (pp 2, 3). Median percentage changes in lathosterol, β-sitosterol, campesterol, and stigmasterol are shown in the appendix (p 4). Median percent changes in FGF-19 were –13·9 (IQR –35·9 to 16·5) in the placebo group, –49·0 (–59·6 to –22·5) in the seladelpar 50 mg group, and –78·1 (–84·7 to –31·8) in the seladelpar

200 mg group. These changes were significant versus placebo (p=0·047 for seladelpar 50 mg and p=0·006 for seladelpar 200 mg; appendix p 12).

There were no deaths during the study and no serious adverse events during the treatment period. Apart from the ALT events previously described, no adverse events were considered severe. The most frequently reported adverse events were pruritus (16%), nausea (13%), diarrhoea (10%) and dyspepsia, muscle spasms, myalgia, and dizziness (each 8%; table 3). There were no apparent differences in the distribution of adverse events between groups apart from the grouping of muscle-related adverse events (myalgia, muscle spasms, and musculoskeletal pain). All adverse evnets are shown in the appendix (pp 8, 9). Six muscle-related adverse events were recorded: one in the placebo group and five in the seladelpar 200 mg group (including a patient who discontinued for a muscle adverse event).

In total, five patients discontinued treatment before the study termination. Three of these were for the grade 3 ALT increases that led to study closure (one patient on seladelpar 50 mg, two on seladelpar 200 mg). Two other patients in the seladelpar 200 mg group discontinued: one because of an increase in creatine associated with muscle pain discussed above, and one was lost to follow-up.

All three grade 3 ALT elevations that led to discontinuation and study termination were judged probably drug related. ALT elevations were similar: rapid onset (identified during the first on-treatment visit at week 2), asymptomatic, and fully reversible 2–4 weeks after treatment discontinuation. There was no eosinophilia or concurrent elevation in total bilirubin. All ALT elevations were associated with decreases in GGT, as well as decreases in alkaline phosphatase (appendix p 13). Two additional patients developed grade 2 ALT elevations that did not lead to treatment interruption. Both patients were on seladelpar 200 mg (appendix p 6).

Pruritus was reported by one patient on placebo, four on seladelpar 50 mg, and one on seladelpar 200 mg. Three pruritus adverse events were considered treatment related: one on placebo, two on seladelpar 50 mg, and none on seladelpar 200 mg. 13 (34%) patients were considered to have pruritus at baseline (as judged with a pruritus visual analogue score ≥30): four on placebo, four on seladelpar 50 mg, and five on seladelpar 200 mg (table 1). At baseline, mean pruritus visual analogue scores were 18 (SD 18) in the placebo group, 21 (22) in the seladelpar 50 mg group, and 33 (25) in the seladelpar 200 mg group. The mean visual analogue scores at end of treatment were 27 (SD 27) in the placebo group, 21 (24) in the seladelpar 50 mg group, and 31 (31) in the seladelpar 200 mg group. The 5D-itch mean total scores at baseline were 11 (SD 4) in the placebo group, 11 (5) in the seladelpar 50 mg group, and 11 (3) in the seladelpar 200 mg group.

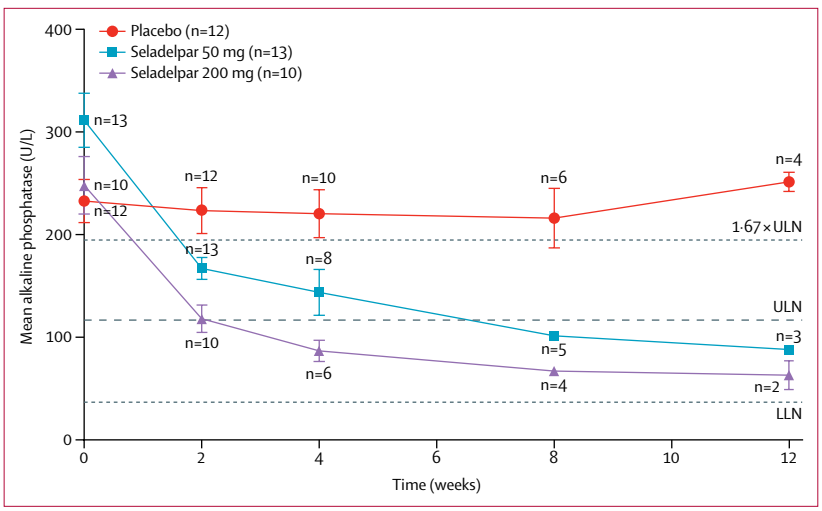

Figure 3: **Mean changes in alkaline phosphatase over 12 weeks for each treatment group**
ULN=upper limit of normal. LLN=lower limit of normal. Bars are SE.

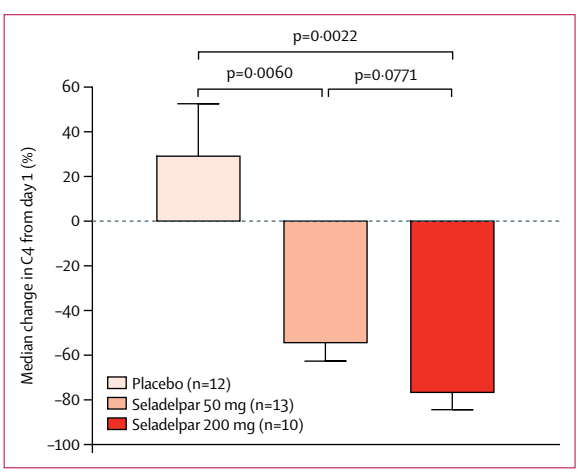

Figure 4: **Median percentage change in 7-α-hydroxy-4-cholesten-3-one (C4) over 12 weeks for each treatment group (last observation carried forward)**
Bars are SE.

At the end of treatment, the 5D-itch mean total scores were 11 (SD 4) in the placebo group, 12 (6) in the seladelpar 50 mg group, and 11 (4) in the seladelpar 200 mg group.

No relevant changes in haematology parameters were recorded. Mean percentage changes in haemoglobin, serum creatinine, and serum homocysteine are presented in the appendix (p 1).

Seladelpar plasma exposure data indicated that trough (pre-dose samples) concentrations did not appear higher than expected, notably for patients with grade 3 aminotransferase elevation (appendix p 14).

Discussion

The objectives of this study were to evaluate the safety and efficacy of seladelpar to lower alkaline phosphatase concentrations in patients with primary biliary

	Placebo group (n=13)		Seladelpar 50 mg group (n=13)		Seladelpar 200 mg group (n=12)	
	Grade 1–2	Grade 3	Grade 1–2	Grade 3	Grade 1–2	Grade 3
Pruritus	1 (8%)	0	4 (31%)	0	1 (8%)	0
Nausea	1 (8%)	0	3 (23%)	0	1 (8%)	0
Diarrhoea	2 (15%)	0	1 (8%)	0	1 (8%)	0
Dizziness	1 (8%)	0	2 (15%)	0	0	0
Dyspepsia	0	0	2 (15%)	0	1 (8%)	0
Muscle spasms	0	0	0	0	3 (25%)	0
Myalgia	1 (8%)	0	0	0	2 (17%)	0
Alanine aminotransferase increased	0	0	0	0	2 (17%)	0
Aspartate aminotransferase increased	0	0	0	0	1 (8%)	1 (8%)
Hepatic enzyme and aminotransferase increased	0	0	1 (8%)	1 (8%)	0	2 (17%)
Oropharyngeal pain	0	0	2 (15%)	0	0	0

No grade 4 or 5 adverse events occurred.

Table 3: **Common Terminology Criteria adverse event categories occurring in two or more individuals per group**

cholangitis showing an inadequate response to ursodeoxycholic acid. Seladelpar is the first potent and selective PPAR-δ agonist to be evaluated in primary biliary cholangitis and the key role played by PPAR-δ in the regulation of bile acid synthesis, inflammation and fibrosis, justified this objective. Seladelpar, originally developed to lower lipids in patients with mixed dyslipidaemia, was also previously associated with consistent decreases in markers of cholestasis, including alkaline phosphatase and GGT.[12]

The study used a dose-ranging, placebo-controlled, double-blind design that has been previously used in this setting, and applied similar eligibility criteria to facilitate comparison with obeticholic acid.[28] Specifically, inadequate responders to ursodeoxycholic acid treatment, according to accepted criteria, were enrolled and seladelpar was used as an add-on therapy. The study intended to exclude patients with decompensated cirrhosis but one randomised patient developed a variceal bleeding complication before receiving any treatment. It is known that some patients with primary biliary cholangitis can develop gastro-oesophageal varices before becoming cirrhotic.[2]

The study was discontinued when about half of the patients were enrolled as a result of three grade 3 increases in ALT levels. The study was stopped to protect patients and because large decreases in GGT and 5′-nucleotidase indicated that the proof-of-concept for activity was likely to have been achieved. Additionally, new results from a rat disposition study revealed that seladelpar and its metabolites were almost exclusively eliminated through bile, which potentially suggested that higher than expected hepatic concentrations of seladelpar might have occurred in patients with primary biliary cholangitis (CymaBay Therapeutics, Newark, CA, USA; data not shown). However, seladelpar treatment, both at the 50 mg and 200 mg doses, elicited large percentage alkaline phosphatase decreases and normalised alkaline phosphatase in all five patients who completed 12 weeks of therapy.

The three cases of grade 3 ALT elevation that led to stopping the study were judged related to seladelpar and were clinically similar. There was a rapid onset of elevation on treatment initiation, a rapid return to baseline concentrations after drug interruption, and the increases were not associated with total bilirubin elevation or signs of idiosyncrasy, such as allergic reaction or eosinophilia. In each case, the aminotransferase elevations were associated with a parallel decrease in markers of cholestasis, such as alkaline phosphatase and GGT. Based on available data, there were no clinical or biological characteristics that could differentiate patients with aminotransferase elevation from the other patients. Examining all cases of ALT elevation during treatment, whether grade 2 or grade 3, there was a suggestion that ALT elevations were dose related, with more cases on seladelpar 200 mg.

The aminotransferase elevations were unexpected, as this was not reported in previous studies in which patients were treated with seladelpar for up to 12 weeks and with daily doses of up to 200 mg.[12,26,27] Thus, this effect could be specific to primary biliary cholangitis and its underlying cholestasis. As mentioned, recent data in rats indicate that seladelpar and its metabolites are almost exclusively excreted into the bile (data not shown). Therefore, increased drug retention in primary biliary cholangitis could have led to higher liver concentrations in this study compared with studies in non-cholestatic patients. Seladelpar trough plasma concentrations did not suggest a higher exposure, either in patients with aminotransferase elevations relative to patients with no elevation, or in the patients with primary biliary cholangitis overall compared with other studies (data not shown). However, only a full pharmacokinetic profile would provide evidence to the hypothesis that seladelpar exposure was unexpectedly increased in patients with primary biliary cholangitis. We also would have to assume that plasma concentrations of seladelpar and its metabolites truly reflect their intra-hepatic concentrations. Alternatively, seladelpar or its metabolites might evoke an immune reaction in patients with primary biliary cholangitis that would not occur in patients who did not have primary biliary cholangitis. Concerning the specific mechanism of the observed aminotransferase elevations, there is currently no further information available to invoke one. Although an acute aminotransferase elevation is usually interpreted as a sign of hepatocyte cytolysis,[29] it is also known that PPAR agonists can upregulate aminotransferase gene expression.[30,31] Post-hoc analyses of stored samples evaluating more specific makers of liver injury[32] is necessary to further explore this issue.

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Animal studies could be useful to determine the relationship between hepatic and plasma concentrations of seladelpar. In this study, the concentrations of chenodeoxycholic acid or lithocholic acid, which have been associated with hepatotoxicity,[33] were not increased compared with baseline, making this mechanism of action unlikely.

Seladelpar did not appear to be associated with drug-induced or worsened pruritus. This feature might, if replicated, differentiate seladelpar from obeticholic acid, as the tolerability of obeticholic acid is limited by this side-effect.[4] However, the size of the current study precludes any conclusion on whether seladelpar might have a beneficial effect on pruritus of primary biliary cholangitis, as has been suggested for bezafibrate.[34]

With regard to other safety parameters, at the 200 mg dose of seladelpar one patient discontinued treatment with muscle pain and increased creatine kinase concentration that were considered treatment related. By contrast with other PPARs, the δ receptor is expressed in muscle. Although such adverse events were not observed with seladelpar when prescribed in patients with homozygous familial hypercholesterolaemia on maximally tolerated statin therapy,[27] caution should be exercised. Seladelpar was also associated with dose-dependent elevations of serum homocysteine and serum creatinine concentrations, which are commonly observed with other PPARs.[35–37] The increase in serum creatinine could be problematic because it is used clinically as a marker of decreased renal glomerular filtration and the glomerular filtration rate is estimated with a formula that is based on serum creatinine concentrations.[38] One patient had an increase in serum creatinine that was considered clinically significant by the investigator. Previous studies have shown that increased serum creatinine associated with some PPAR agonists, such as PPAR-α, pan-PPAR, or mixed PPAR-α/δ, was neither linked to relevant decrease in measured glomerular filtration rate nor to changes in measured creatinine clearance, because serum creatinine and creatinine urinary excretion increased in similar proportions.[39] Long-term prospective studies of fenofibrate, a PPAR-α agonist, in patients with diabetes with compromised renal function, did not show a negative effect on renal function, despite small increases in serum creatinine.[40] Finally, increases in serum creatinine associated with PPARs, as seen in the current study, are reversible,[41] which rules out permanent kidney damage. The PPAR-mediated increase in serum creatinine has been postulated to result from an increased release of creatine from muscle. Creatine is stored in muscles to supply energy and is rapidly converted to creatinine in the serum.[42]

All five patients who received seladelpar for 12 weeks normalised their alkaline phosphatase concentrations. This activity in patients who are inadequate responders to ursodeoxycholic acid appears greater than that seen with obeticholic acid in a similarly designed phase 2 study.[28] By contrast with the aminotransferase elevations, seladelpar's activity was not dose related, and the effect seemed already maximal at 50 mg, which calls for the exploration of lower doses to optimise the risk–benefit ratio of the drug. The decrease in alkaline phosphatase was also associated with decreases in other markers of cholestasis, including GGT and 5′-nucleotidase, and the 50 mg dose of seladelpar was also associated with decreases in total bilirubin concentrations. Similar to ursodeoxycholic acid and obeticholic acid,[2,28] the concentrations of markers of cholestatic injury returned to baseline concentrations when seladelpar treatment was stopped.

The study has some important limitations. Because the study was discontinued before its completion and because of its small sample size, these data are preliminary and should be confirmed in larger studies. The conclusion regarding alkaline phosphatase normalisation is only based on five patients who have reached 12 weeks of treatment, and the aminotransferase elevation was concerning enough to terminate the study. Nevertheless, the normalisation of alkaline phosphatase with seladelpar, if confirmed at lower doses in the absence of a safety signal, offers promise for a new treatment approach in patients with primary biliary cholangitis who do not respond fully to ursodeoxycholic acid therapy.

This study provides evidence regarding the mechanism of action of seladelpar. First, there was a striking effect on hepatocyte bile acids synthesis as shown by a decrease in serum C4 concentrations, a reliable marker of the activity of 7α-hydroxylase which hydroxylates cholesterol in position 7 and constitutes the rate-limiting step in bile acids synthesis by the classical pathway.[43] The decrease in C4 concentrations was not meaningfully different between the two seladelpar doses. The C4 data were corroborated by a decrease in 7α-hydroxy-cholesterol and by decreases in cholic acid concentrations, the product of the classic pathway, and further by decreases in deoxycholic acid, a metabolite of cholic acid.[44] Additional reductions in hepatic bile acids might have resulted from decreases in cholesterol absorption and decreases in cholesterol synthesis intermediates. Overall, these data suggest that seladelpar can reduce bile acid concentrations by decreasing their synthesis as well as decreasing the availability of cholesterol as a substrate for their synthesis. Treatment with ursodeoxycholic acid increases transport of bile acids into the canalicular space, which is believed to be hepatoprotective due to the lowering of bile acid concentrations within hepatocytes.[45] Seladelpar's inhibition of bile acid metabolism might therefore potentiate this beneficial effect by further lowering hepatocyte concentrations of bile acids. Additionally, seladelpar-induced decreases in hs-CRP are consistent with anti-inflammatory activity of the drug, an action first demonstrated in patients with obesity and mixed dyslipidaemia.[12] Finally, the decreases in FGF-19

concentrations seen with seladelpar indicate that its action is not mediated through farnesoid X receptor agonism as is the case for obeticholic acid.[4] It has also been suggested that FGF-19 might play a role in the development of hepatocellular carcinoma and that its expression is induced in the liver under cholestatic and cirrhotic conditions.[46] As in the case with other chronic liver diseases, patients with primary biliary cholangitis are at an increased risk of hepatocellular carcinoma,[1,2] and the decreased concentrations of FGF-19 induced by seladelpar could be of interest.

In conclusion, this study demonstrated that seladelpar, at both the 50 mg and 200 mg daily doses, has the potential to normalise biochemical markers of cholestasis in patients with primary biliary cholangitis who have inadequately responded to ursodeoxycholic acid. However, treatment with seladelpar was associated with aminotransferase elevations and, consequently, the study was interrupted before completion. Since the elevation of aminotransferases was more frequent at 200 mg compared with 50 mg, while the anti-cholestatic activity was independent of doses, lower doses of seladelpar should be explored to optimise the risk–benefit ratio in patients with primary biliary cholangitis. A study of low-dose seladelpar in patients with primary biliary cholangitis has been initiated (NCT02955602 and EudraCT 2016-002996-91).

Contributors

Y-JC, AS, MV, HC, RM, CAM, and PFB contributed to the study design, data collection, analysis, and the operation of the study. DJ, CLB, MRG, BRB, YD, NG, SCG, JAO, DS, M-AW, VC, LC, HH, MEJ, AEK, GFM, PB, BLF, CL, JMV, DEB, MH, EJ, FR, HS, MLS, JHS, and GMH were investigators in the study. DJ, PFB, MGS, CLB, and GMH finalised data presentation and had responsibility to submit the manuscript after obtaining agreement from all the authors.

Declaration of interests

DJ reports grants and personal fees from Intercept. Intercept, GlaxoSmithKline, Novartis, Cymabay, FFPharma, Shire, and Pfizer are all UK-PBC partners, for which DJ is project director. PFB is an employee of CymaBay Therapeutics and owns options to buy shares of the company. PFB is named on a CymaBay Therapeutics patent covering the use of MBX-8025 (seladelpar) for the treatment of primary biliary cholangitis. MGS reports grants and personal fees from Gilead, grants and personal fees from Intercept, and grants and fees from CymaBay, Merck, Abbvie, BMS, GRI Inc, Allergan/Tobira, Novartis, GlaxoSmithKline, Genfit, and Novo-Nordisk, outside the submitted work. CLB has participated in research with Intercept Pharmaceuticals, NGM Biosciences, Gilead, Takeda, BMS, GlaxoSmithKline, Galectin Therapeutics, and CymaBay. CLB is on the advisory board of Intercept Pharmaceuticals, GlaxoSmithKline, and Takeda and on the speakers bureau of Intercept Pharmaceuticals. YD reports other [A: de[illegible]her] from CymaBay Therapeutics, during the conduct of the study. NG has received a grant from, and is on the speakers bureau for, Intercept Pharmaceuticals. SCG reports grants from AbbVie Pharmaceuticals, Exalenz, Gilead Pharmaceuticals, Intercept Pharmaceuticals, and Merck, and grants and fees from AbbVie Pharmaceuticals, CVS Caremark, Gilead Pharmaceuticals, and Merck, outside the submitted work. JAO received payments from CymaBay for this trial, and is an advisory board member for Intercept Pharmaceuticals. VC reports receipt of grants from CymaBay Therapeutics. AEK reports grants and personal fees from Intercept Pharmaceuticals, and personal fees from Falk Pharma, GlaxoSmithKline, MSD, and Beiersdorf. GFM reports grants from Medical Research Council and National Institute for Health Research Rare Diseases—Translational Research Collaboration. GFM works with a collaborating centre in Intercept-sponsored Clinical Trial of an Investigational Medicinal Product (CTIMP) and Novartis-sponsored CTIMP. BLF reports grants from CymaBay Therapeutics and Intercept, and speakers bureau fees from Intercept. CL reports grants and personal fees from Intercept, grants from Gilead, grants and personal fees from Novartis, grants from NGM, grants from Shire, grants from GlaxoSmithKline, and grants and personal fees from TARGET PharmaSolutions. JMV reports grants from Intercept, personal fees from Intercept, grants from Genfit, grants from Gilead, and personal fees from Gilead. EJ reports personal fees from CymaBay Therapeutics, and has served as a lecturer, consultant, or investigator for AbbVie, Gilead, Bristol-Myers Squibb, MSD, and Roche. HS reports personal fees from Intercept. MLS reports grants from CymaBay, grants and personal fees from Gilead, and grants from NGMBio. MV and HC are employees of CymaBay Therapeutics and own options for its stock. CAM is an employee of CymaBay Therapeutics and owns stock and is an option grantee for the company. GMH has consulted for GlaxoSmithKline, Novartis, Intercept, Univar, and Falk. MRG, BRB, DS, M-AW, LC, HH, PB, DEB, MH, FR, JHS, Y-JC, AS, RM, and MEJ declare no competing interests.

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